

Remarks

The Office Action dated October 6, 2008 has been carefully reviewed and the following comments are made in response thereto. Claims 1-6, 8-32 and 34-40 are pending in the instant application. Claims 9-32 and 35-39 have been withdrawn by the Examiner as allegedly being drawn to non-elected inventions. Claims 4, 5 and 40 are amended. Applicants submit that the amendments to the claims do not introduce any prohibited new matter.

Rejections Under 35 U.S.C. 112, first paragraph (enablement)

Claims 1-6, 8, 34 and 40 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. Applicants respectfully traverse this rejection for at least the reasons stated below.

Enablement is a legal determination that assesses whether a specification teaches one of skill in the art to make and use what is claimed. Enablement is not precluded even if some experimentation is necessary, as long as the amount of experimentation is not undue. *Atlas Powder Co. v. E. I. Du Pont De Nemours Co.*, 750 224 USPQ 409, 3 (Fed. Cir. 1984); *W. L. Gore and Associates v. Inc.*, 721 220 USPQ 303, 315 (Fed. Cir. 1983).

Nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples. *In re Marzocchi*, 439 220, 223, 169 USPQ 367, 369 (CCPA 1971). An analysis of whether the rejected claims are supported by an enabling disclosure requires a determination of whether that disclosure contained sufficient information regarding the subject matter of the claims to teach one of skill in the art how to make and use what is claimed. "[I]t is not a function of the claims to specifically exclude either possible inoperative substances or ineffective reacting proportions." *In Application of Dinh-Nguyen*, 492 F.2d 865 at 858-9 181 USPQ 46 (CCPA (1974)). Thus, a claim is not too broad because it does not explicitly exclude every conceivable unworkable application of the method, providing it enables one of skill in the art to practice what is claimed in its workable applications.

Notably, to establish a *prima facie* case of lack of enablement, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for what is claimed. *In re Wright*, 999 1557, 1561-62, 27 1510, 1513 (Fed. Cir. 1993). (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). See also *Morehouse*, 545 162, 192 USPQ 29 (CCPA 1976). The threshold step in resolving this issue is to determine whether the Examiner

has met this burden of proof by advancing acceptable reasoning inconsistent with enablement. "Factors to be considered by the examiner in determining whether disclosure would require undue experimentation have been summarized in *In re Wands*, 858 F.2d 1068, 1073, 81 USPQ2d 1861, 1868 (Fed. Cir. 1988) and are outlined in the Guidelines. These factors include: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the claimed subject matter, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. All factors must be considered. A deficiency in meeting one factor does not preclude a finding of enablement. Consideration of a single factor or fewer than all is not dispositive.

The Examiner has alleged that the instant claims are not enabled by the present disclosure because: (1) the claims are overly broad, (2) the amount of experimentation required is undue, (3) the specification lacks specific guidance for making the claimed invention, (4) the specification lacks the presence of working examples and (5) the art was highly unpredictable at the time of the instant invention (Office Action at page 12). Each of the Examiner's alleged reasons for lack of enablement will be addressed in turn.

(1) Breadth of the Claims

The Examiner alleged that the claims encompass any and all bacterial surface layer proteins, comprising any internal insertion of any heterologous polypeptide where said modified S-protein is able to crystallize (Office Action at page 9).

Applicants respectfully submit that the instant claims are not as broad as interpreted by the Examiner. Applicants point out that the instant claims are limited to S-proteins from a *Lactobacillus* bacterium, which proteins are from 40 to 70 kd in size and highly basic with a pI of at least 9. As such, the claims are narrowly focused as demonstrated by the Declaration of Dr. Pieter Pouwels dated December 11, 2007 and Amendment and Response filed April 28, 2008.

(2) Quantity of Experimentation Necessary

The Examiner alleged that the quantity of experimentation required to practice the instant invention would be undue because it cannot be predicted from the instant disclosure how to make/use the claimed genus of S-layer proteins with an inserted heterologous polypeptide (Office Action at page 12).

The instant specification describes in abundant detail how to make and use the claimed proteins (see, e.g., Examples, including pp. 44-45 and Table 1). In addition, Applicants specifically exemplify the insertion of polypeptides at a multiplicity of different amino acid positions in the S-protein of a *Lactobacillus* bacterium (see, e.g., Table 1, page 45). Notably, Applicants have discovered that polypeptides can be inserted in variable, non-conserved regions of S-proteins that do not have any predicted secondary structure elements and thus, polypeptides inserted into these regions result in retention of the ability of the protein to crystallize (see, e.g., Examples, including pp. 44-45 and Table 1). For example, a polypeptide can be inserted at a position from amino acids 1 to 20; at a position from amino acids 35 to 55; at a position from amino acids 100 to 130; at a position from amino acids 110 to 140; at the position of amino acid 193; and/or at a position from amino acids 340 to 360 (see, e.g., specification at page 7). Therefore, it would not require undue experimentation for a skilled artisan to insert a heterologous polypeptide into numerous positions in a S-protein as specified by the instant disclosure and as claimed.

(3) Direction or Guidance Provided in the Specification

The Examiner alleged that the instant specification does not provide specific guidance for which bacterial surface layer proteins will crystallize when the modification comprises any internal insertion of a heterologous polypeptide. Specifically, the Examiner asserted that the instant specification does not provide a baseline sequence to enable a skilled artisan to modify any S-layer protein (Office Action at pages 9-10).

Applicants respectfully submit that the instant specification demonstrates the insertion of polypeptides at a multiplicity of different amino acid positions in the S-protein of a *Lactobacillus* bacterium (see, e.g., Table 1, page 45). The instant Specification demonstrates that insertions within the regions specified by claim 1 result in retention of the ability of the modified proteins to crystallize (see, e.g., Examples, including pp. 44-45 and Table 1). Thus, claim 1 specifies regions where insertions may be made and the Examples of the application show the regions to be effective (see, e.g., specification at pages 44-45).

Furthermore, Applicants respectfully submit that S-layer proteins are highly conserved (e.g., primary, secondary and tertiary structures). For example, Applicants point out that *L. acidophilus* shares a similar tertiary structure to *L. helveticus*, *L. crispitus*, and *L. gailinarum*. In fact, the tertiary structure from all four of these representative species from the *Lactobacillus* genus may be superimposed and the sequence of these related polypeptides can be aligned

and used to locate an insertion site for a heterologous peptide (see, e.g., Office Action Response dated November 15, 2007). For example, a skilled artisan could superimpose the secondary or tertiary structure or align the primary sequence from any specie from the *Lactobacillus* genus (e.g., SEQ ID NO: 2) to determine which residues in the specie correspond to a position from amino acids 1 to 20, a position from amino acids 35 to 55, a position from amino acids 100 to 130, a position from amino acids 110 to 140, the position of amino acid 193 or a position from amino acids 340 to 360 described in the instant specification. Therefore, the instant specification clearly enables a skilled artisan to insert a polypeptide into numerous positions in a S-protein.

(4) Presence or Absence of Working Examples

The Examiner alleged that the instant specification does not provide any working examples to rectify the missing information in the instant specification pertaining to the claimed variant proteins (Office Action at page 10).

Applicants respectfully submit that the instant specification provides numerous examples for inserting a heterologous polypeptide at a site in a bacterial S-protein, which insertion permits the S-protein to crystallize (see, e.g., Table 1). Applicants have described a multiplicity of modified S-proteins with inserted polypeptides that can still crystallize. Notably, Applicants have discovered that polypeptides can be inserted in variable, non-conserved regions of the S-proteins that do not have any predicted secondary structure elements. Thus, a heterologous polypeptide can be inserted into an S-protein as claimed and the insertion does not prevent crystallization. Given that Applicants have provided guidance as to the positions in the S-protein where such insertions may be made, a sufficient number of working examples have been described.

(5) State of the Prior Art

The Examiner alleged that protein chemistry is one of the most unpredictable areas of biotechnology and consequently the effects of sequence dissimilarities upon protein structure and function cannot be predicted. The Examiner pointed to Bowie *et al.* (*Science* (1990) 257:1306-1310) ("Bowie") reciting that positions within a protein's sequence where amino acid substitutions can be made with a reasonable expectation of maintaining function are limited because certain regions are critical to the three dimensional structure of the protein (Office Action at page 11).

As stated by Dr. Pieter Pouwels, *Bowie* is concerned with whether insertion of foreign amino acid sequences in a protein will change the protein's three dimensional structure and thus change the ability of the protein to form a three dimensional crystal structure of the type used in X-ray crystallography (see, e.g., Declaration of Dr. Pieter Pouwels dated December 11, 2007). In addition, different *Lactobacillus* surface layer proteins possess similar primary sequences and similar three-dimensional structures (Office Action Response mailed April 28, 2008). For example, Applicants point out that *L. acidophilus* shares a similar tertiary structure to *L. helveticus*, *L. crispitus*, and *L. gallinarum*. In fact, the tertiary structure from all four of these representative species from the *Lactobacillus* genus may be superimposed (see, e.g., Office Action Response mailed November 15, 2007). As such, *Bowie* does not impact the ability for one of skill in the art to make and use the instant invention because a skilled artisan would have predicted that S-proteins from different *Lactobacillus* species would behave in a comparable manner.

For the above-enumerated reasons (1) to (5), Applicants submit that the instant claims are enabled by the specification. Nonetheless, Applicants point out that the Wands factors described above must be considered together and that the lack of any one factor is not dispositive on the issue of enablement. Accordingly, Applicants request that the rejection of claims 1-6, 8, 34 and 40 under 35 U.S.C. 112, first paragraph be reconsidered and withdrawn.

Rejections Under 35 U.S.C. 112, first paragraph (written description)

Claims 1-6, 8, 34 and 40 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. Applicants respectfully traverse this rejection for at least the reasons set forth below.

The purpose behind the written description requirement is to ensure that the patent applicant had possession of the claimed subject matter at the time of filing of the application *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). A specification must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, i.e., whatever is now claimed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ.2d 1111, 1117 (Fed. Cir. 1991). A written description requirement issue generally involves the question of whether the subject matter of a claim is supported by or conforms to the disclosure of an application as filed. The test for sufficiency of support in a patent application is whether the disclosure of the application relied upon

"reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting *In re Kaslow*, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)) (see also, MPEP 2163.02).

The written description for a claimed genus can be satisfied by description of a representative number of species by disclosure of identifying characteristics, including structural and physical characteristics, functional characteristics coupled with known or disclosed correlation with structural characteristics or a combination of such factors sufficient to demonstrate that the applicant was in possession of the claimed subject matter. MPEP § 2163; see *University of California v. Eli Lilly*, 119 F. 3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Further, the standard is an objective one, based on what one of skill in the art would recognize in the disclosure and whether "the description clearly allows persons of skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d at 1008, 1012. Thus, the knowledge and level of skill in the particular art is a factor to be considered in determining the standard. For example, there is no per se rule to provide sequence information when that sequence is already known in the field. *Capon v. Eshhar v. Dudas* 418 F.3d 1349 (Fed. Cir. 2005); *Falkner v. Inglis* 448 F.3d 1357, 1367-68.

The Examiner has alleged that the instant claims fail to comply with the written description requirement. Specifically, the Examiner stated that the instant application fails to (1) describe a baseline sequence for a S-protein, (2) fails to describe an undetermined number of insertion positions in a S-protein, and (3) fails to describe a sufficient number of representatives from the claimed genus. Each of the Examiner's alleged reasons for lack of written description will be addressed in turn.

(1) Alleged requirement for a baseline sequence

The Examiner alleged that without a baseline sequence for the surface layer protein one of skill in the art would not be able to identify which polypeptide will encode a S-protein having the ability to crystallize and form a crystalline monolayer, where the insertion site of the heterologous polypeptide is (i) at a position from amino acids 1 to 20;(ii) at a position from amino acids 35 to 55;(iii) at a position from amino acids 100 to 130;(iv) at a position from amino acids 110 to 140;(v) at the position of amino acid 193; and/or (vi) at a position from amino acids 340 to 360 as recited in the instant claims (Office Action at page 14).

Applicants respectfully submit that S-layer proteins from *Lactobacillus* are highly conserved and thus represent a tightly defined group of proteins (see, e.g., Declaration of Dr. Pieter Pouwels dated December 11, 2007). Applicants respectfully submit that S-layer proteins are highly conserved (e.g., primary, secondary and tertiary structures). For example, Applicants point out that *L. acidophilus* shares a similar tertiary structure to *L. helveticus*, *L. crispitus*, and *L. gallinarum*. In fact, the tertiary structure from all four of these representative species from the *Lactobacillus* genus may be superimposed and the sequence of these related polypeptides can be aligned and used to locate an insertion site for a heterologous peptide (see, e.g., Office Action Response dated November 15, 2007). For example, a skilled artisan could superimpose the secondary or tertiary structure or align the primary sequence from any specie from the *Lactobacillus* genus (e.g., SEQ ID NO: 2) to determine which residues in the specie correspond to a position from amino acids 1 to 20, a position from amino acids 35 to 55, a position from amino acids 100 to 130, a position from amino acids 110 to 140, the position of amino acid 193 or a position from amino acids 340 to 360 described in the instant specification.

(2) Alleged undetermined number of insertion positions in a S-protein

The Examiner alleged that the instant claims encompass a multiplicity of insertion positions as described in the Examples and thus the claims are drawn to an undetermined number of insertion positions which have not been adequately described. Thus, the Examiner argues that it is not known if S-proteins with polypeptides inserted at other sites will be able to crystallize to form a crystalline monomer.

Applicants respectfully submit that the instant specification fully describes the insertion of polypeptides at a multiplicity of different amino acid positions in the S-protein of *Lactobacillus* bacteria (see, e.g., Table 1, page 45). Notably, Applicants have discovered that polypeptides can be inserted in variable, non-conserved regions of the S-proteins, without any predicted secondary structure elements, and the ability to crystallize is retained. For example, a polypeptide can be inserted as claimed at a position from amino acids 1 to 20; at a position from amino acids 35 to 55; at a position from amino aids 100 to 130; at a position from amino acids 110 to 140; at the position of amino acid 193; and/or at a position from amino acids 340 to 360 (see, e.g., specification at page 7). Therefore, the instant specification clearly provides a skilled artisan sufficient information to insert a polypeptide into numerous positions in a S-protein.

(3) Alleged insufficient number of representatives from the claimed genus

The Examiner alleged that the instant specification fails to describe a representative number of S-proteins with inserted heterologous polypeptides that can still crystallize. Specifically, the Examiner stated that the specification needs to provide guidance as to which heterologous peptides/proteins can be inserted at a given position within a given S-protein and not effect crystallization (Office Action at page 17).

Applicants respectfully submit that the instant specification describes a multiplicity of modified S-proteins with inserted polypeptides that can still crystallize. Notably, primary and secondary sequence analysis reveals that the S-proteins from *Lactobacillus* are similar to the extent that they are expected to have the same folding (see, e.g., Declaration of Dr. Pieter Pouwels dated December 11, 2007). The fact that other S-layer proteins behave in a similar manner is strengthened by the literature after the filing of the instant application which demonstrates that the insertion of foreign epitopes in the surface layer results in surface display of these epitopes and leaves the S-layer intact (see, e.g., Declaration of Dr. Pieter Pouwels dated December 11, 2007). Moreover, the instant specification provides that the inserted polypeptides can be 5, 10, 15, 20, 30 or 40 amino acids in length (see, e.g., specification at page 26). Also, the specification describes examples of numerous polypeptides of varying length that have been inserted into a S-protein without affecting crystallization (see, e.g., specification, Table 1, page 45). Thus, Applicants have described a representative number of species of S-proteins with inserted polypeptides.

For the above-enumerated reasons (1) to (3), Applicants submit that the specification provides adequate written description for the instant claims. Accordingly, Applicants request that the rejection of claims 1-6, 8, 34 and 40 under 35 U.S.C. 112, first paragraph be reconsidered and withdrawn.

Claim 40 was rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. In particular, the Examiner alleges that the recitation of "at a position from amino acids 290 to 410" constitutes new matter (Office Action at page 19).

Without acquiescing to the merits of the Examiner's rejection, and solely to expedite prosecution of the instant application, Applicants have amended claim 40 to replace the phrase "at a position from amino acids 290 to 410" with "at a position from amino acids 320-410." Exemplary support for this amendment may be found in the specification at page 7. As such, claim 40 does not contain any prohibited new matter. Accordingly, Applicants respectfully

request that the rejection of claim 40 under 35 U.S.C. 112, first paragraph be reconsidered and withdrawn.

Rejections Under 35 U.S.C. 112, second paragraph

Claims 1-6, 8, 34 and 40 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite. In particular, the Examiner alleged that claims 1 and 40 use the phrase "at a position from amino acids x to y," and thus it is unclear as to what is meant since no baseline sequence is recited (Office Action at page 20). Applicants respectfully traverse this rejection for at least the reasons set forth below.

Claims are not read in a vacuum but instead are considered in light of the specification and the general understanding of the skilled artisan. *Rosemount Inc. v. Beckman Instruments, Inc.*, 727 F.2d 1540, 1547, 221 USPQ 1, 7 (Fed. Cir. 1984), *Caterpillar Tractor Co. v. Berco, S.P.A.*, 714 F.2d 1110, 1116, 219 USPQ 185, 188 (Fed. Cir. 1983). Claim language is satisfactory if it reasonably apprises those of skill in the art of the bounds of the claimed invention and is as precise as the subject matter permits. *Shatterproof Glass Corp. v. Libby-Owens Ford Col.*, 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir.), cert. dismissed, 106 S.Ct. 340 (1985).

Applicants respectfully submit that S-layer proteins are highly conserved (e.g., primary, secondary and tertiary structures). For example, Applicants point out that *L. acidophilus* shares a similar tertiary structure to *L. helveticus*, *L. crispitus*, and *L. gallinarum*. In fact, the tertiary structure from all four of these representative species from the *Lactobacillus* genus may be superimposed and the sequence of these related polypeptides can be aligned and used to locate an insertion site for a heterologous peptide (see, e.g., Office Action Response dated November 15, 2007). For example, a skilled artisan could superimpose the secondary or tertiary structure or align the primary sequence from any specie from the *Lactobacillus* genus (e.g., SEQ ID NO: 2) to determine which residues in the specie correspond to a position from amino acids 1 to 20, a position from amino acids 35 to 55, a position from amino acids 100 to 130, a position from amino acids 110 to 140, the position of amino acid 193 or a position from amino acids 340 to 360 described in the instant specification. Accordingly, Applicants respectfully request that the rejection of claims 1-6, 8, 34 and 40 under 35 U.S.C. 112, second paragraph be reconsidered and withdrawn.

Claim 40 was also rejected under 35 U.S.C. 112, second paragraph, as being indefinite. In particular, the Examiner alleged that the phrase "at a position from amino acids from amino acids 290-410," is unclear (Office Action at page 20).

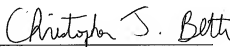
Without acquiescing to the merits of the Examiner's rejection, and solely to expedite prosecution of the instant application, Applicants have amended claims 40 to remove the duplicative language. Accordingly, Applicants respectfully request that the rejection of claim 40 under 35 U.S.C. 112, second paragraph, be reconsidered and withdrawn.

Conclusion

Except for issues payable under 37 C.F.R. 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 02-1818. This paragraph is intended to be a constructive petition for extension of time in accordance with 37 C.F.R. 1.136(a)(3). In view of the amendments and arguments presented herein and the previously submitted declaration of Dr. Pieter Pouwels, Applicants respectfully submit that the instant claims are in condition for allowance.

Respectfully submitted,

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Dated: April 6, 2009